C5-

contribution to toxicity, or a substantially reduced functional contribution to toxicity.

Claim 51 (New). A prophylactic or therapeutic vaccine comprising an immunologically effective amount of a recombinantly produced *H. pylori* CT polypeptide, wherein said recombinantly produced polypeptide exhibits substantially no toxicity, or substantially reduced toxicity, and a pharmaceutically acceptable carrier.

C6 Sub D4 cont.

Claim 52 (New). The method of claim 50, wherein the second polypeptide comprises SEQ ID NO:5, or a fragment thereof, which second polypeptide: (i) comprises at least about ten amino acids, (ii) can induce the production of antibodies to *Helicobacter pylori*, and (iii) exhibits no functional contribution to toxicity, or a substantially reduced functional contribution to toxicity.

REMARKS

The Official Action dated February 7, 2000 has been carefully reviewed. In view of the amendments presented herewith and the following remarks, favorable reconsideration and allowance of this application are respectfully requested.

Status of the Claims

Claims 38 - 50 were pending in the application.

Claims 38 - 50 have been rejected.

By way of this amendment, claims 41, 44, and 47 have been canceled without prejudice, claims 38 - 40, 42, 43, 45, 46, and 48 - 50, have been amended, and new claims 51 and 52 have been added.

Upon entry of this amendment claims 38 - 40, 42, 43, 45, 46, and 48 - 52 will be pending.

Summary of the Amendment

The specification has been amended to update the status of the priority and continuing applications.

Applicants respectfully request the Examiner to enter the amendments to the specification (filed February 11, 2000 as a Second Preliminary Amendment) identifying the nucleotide sequences appearing at page 49, line 39, and at page 50, line 1. For the Examiner's convenience, a copy of the Second Preliminary Amendment is attached hereto.

The specification has been amended to provide proper SEQ ID NOS to the sequences appearing at page 53, line 8. The specification has been amended to correct other informalities and typographical errors. An abstract has also been provided. No new matter has been added.

Pursuant to 37 C.F.R. §1.85(c), formal drawings will be filed upon a receipt of a Notice of Allowance.

Claims 38 - 40, 42, 43, 45, 46, and 48 - 50 have been amended to clarify and more accurately describe that which is claimed. Support for these amendments is found throughout the specification (for example, at page 5, lines 31 -35, at page 7, line 38 through page 8, line 12, at page 14, lines 21 - 30, and at page 40, lines 30 - 36) and in the claims as originally filed. No new matter has been added.

New claims 51 and 52 have been added to refer to specific embodiments of the invention. Support for new claims 51 and 52 is found in the original claims, and throughout the specification as originally filed, for example, at page 3, line 31 through page 4, line 8, and page 38, line 31 through page 39, line 7. No new matter has been added.

A substitute Sequence Listing is also provided, listing all SEQ ID NOS (1 through 10) appearing in the specification as amended. SEQ ID NOS:1-8 are those listed in the substitute

Sequence Listing, filed with the Second Preliminary Amendment of February 11, 2000, which amendment was not entered prior to the present Official Action. Applicants respectfully request that the Examiner insert the currently provided, substitute Sequence Listing in place of the substitute Sequence Listing of February 11, 2000. SEQ ID NOS:1 and 8 are now designated as "artificial" in the Sequence Listing, a designation supported in the specification at page 49, line 37 through page 50, line 3. SEQ ID NOS:9 and 10 identify two amino acid sequence motifs presented at page 53, line 8 of the specification. A paper copy of the substitute Sequence Listing is attached hereto. Also provided is a diskette containing a computer readable form of the substitute Sequence Listing. The information recorded in the computer readable form is identical to the paper copy of the substitute Sequence Listing.

Additionally provided herewith is the unexecuted Declaration of Dr. Giuseppe Del Giudice pursuant to 37 C.F.R. §1.132. A substantially identical, executed Declaration will be forwarded in due course.

Rejections under 35 U.S.C. §112, second paragraph

The Examiner has rejected claims 40 - 50 under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter of the invention.

The Examiner objects to the use of the term "substantially" as an allegedly relative term lacking a comparative basis. This term appears in claims 40 (from which claims 41 and 42 depend), 43 (from which claims 44, 45, and 46 depend), 46 (from which claims 47 and 48 depend), 49 (from which claim 50 depends), 50. The rejection on this basis is rendered moot with respect to claims 41, 44, and 47, which have been canceled without prejudice. This term also appears in claim 38 (from which claim 39 depends), claim 39, as amended, and in new claims 51 and 52.

The "distinctly claiming" requirement of 35 U.S.C. §112, second paragraph will be met "if the claims, read in light of the specification, reasonably apprise those skilled in the art both

of the utilization and scope of the invention." *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 U.S.P.Q. 81, 94 (Fed. Cir. 1986) *quoting, Shatterproof Glass Corp. v. Libbey Owen Ford Co.*, 225 U.S.P.Q. 634, 641 (Fed. Cir. 1985). "The term 'substantially' is often used in conjunction with another term to describe a particular characteristic of a claimed invention." M.P.E.P. §2173.05(b). Definiteness will be found for the use of "substantially" where there are general guidelines in the specification (*In re Mattison*, 184 U.S.P.Q. 484 (C.C.P.A 1975)), or one of ordinary skill in the art would know what was meant by the use of the term (*Andrew Corp. v. Gabriel Electronics*, 6 U.S.P.Q.2d 2010 (Fed. Cir. 1988)).

One of ordinary skill in the art would understand the phrases "exhibits substantially no toxicity, or substantially reduced toxicity" and "exhibits no functional contribution to toxicity, or a substantially reduced functional contribution to toxicity," as used in the claims, as amended, to describe *H. pylori* cytotoxin (CT) polypeptides and cytotoxin associated immunodominant (CAI) antigen polypeptides, respectively, to mean that the polypeptide, or fragment thereof, does not exhibit statistically significant cytotoxic effects, and would thus be acceptable for use in human vaccines. The specification describes the known cytotoxic activity of the CT protein at page 2, lines 16 - 17, at page 5, lines 37 - 38, and at page 46, lines 21 - 29. The Declaration of Dr. Del Giudice ("Declaration"), at ¶ 7, further substantiates that the term "substantially," as used to describe the claimed subject matter, provides a definite meaning to one of skill in the art. *In re Alton*, 37 U.S.P.Q.2d 1578 (Fed. Cir. 1996). Applicants respectfully request an affidavit under 37 C.F.R. §1.104(d)(2), if this rejection is maintained.

The Examiner further states that the phrase "an effective amount" is allegedly unclear as to the desired effect. All claims containing the phrase "an effective amount" (claims 43, 46, 49, and 50) have now been amended to contain the phrase "an immunologically effective amount." Support for this amendment can be found at page 41, lines 30 - 36 of the specification. Thus, claims 43, 46, 49, and 50 and the claims depending from them, are now clarified in meaning as to the purpose for which the amount is to be effective.

The Applicants respectfully request that the rejection of claims 40 - 50 under 35 U.S.C. §112, second paragraph be withdrawn.

Rejections under 35 U.S.C. §112, first paragraph

The Examiner has rejected claims 40 - 50 under 35 U.S.C. §112, first paragraph as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art, that the inventors had possession of the claimed invention at the time of filing of the application.

The Examiner has invited Applicants to point to the page and line number in the specification where support for the phrase "exhibits substantially no contribution to toxicity" can be found. As amended, none of the claims contains the phrase "exhibits substantially no contribution to toxicity." Claims 38, 39, and 40, which provide CT polypeptides, or fragments thereof, and claims 43 and 49, which provide vaccines comprising CT polypeptides, or fragments thereof, or methods of preparing such vaccines, now recite "exhibits substantially no toxicity, or substantially reduced toxicity" in the place of the phrase "exhibits substantially no contribution to toxicity." New claim 51, which provides a vaccine comprising a CT polypeptide, also recites the phrase "exhibits substantially no toxicity, or substantially reduced toxicity." Support for the phrase "exhibits substantially no toxicity, or substantially reduced toxicity" can be found in original claim 8 of the application as filed. The specification has been amended accordingly at page 4, line 1, to recite the phrase.

Additionally, claim 46, which provides a vaccine comprising a second polypeptide comprising CAI, or a fragment thereof, and claim 50, which provides a method of preparing such a vaccine, now recite the phrase "exhibits no functional contribution to toxicity, or a substantially reduced functional contribution to toxicity" in place of the phrase "exhibits substantially no contribution to toxicity." New claim 52, which provides a method of making a vaccine comprising a second polypeptide comprising the SEQ ID NO:5 CAI, or fragment thereof, also recites the phrase

"exhibits no functional contribution to toxicity, or a substantially reduced functional contribution to toxicity." Support for the phrase "exhibits no functional contribution to toxicity, or a substantially reduced functional contribution to toxicity" can be found in original claim 9 of the application as filed. The specification has been amended accordingly at page 4, line 1, to recite the phrase. Withdrawal of the rejection on this basis is respectfully requested.

The Examiner has objected to claims which specify "five to about fifteen amino acids," and alleges that the upper limit is not supported in the specification. Claims 42, 45, and 48, as amended, specify a lower limit of "at least about fifteen amino acids." Claims 42, 45, and 48, as amended, therefore, encompass polypeptides of at least 15 amino acids or greater, which is supported in the specification at page 14, lines 21 - 30. Withdrawal of the rejection on this basis is respectfully requested.

The Examiner has rejected claims 40 - 50 and alleges, at page 3 of the Official Action, that Applicants do "not reasonably provide enablement for an amino acid sequence which 'exhibits substantially no contribution to toxicity' or the 'prophylactic or therapeutic vaccine' recitations in the claims."

Applicants respectfully submit that there is insufficient evidence to support the rejection as set forth in the Official Action. Regardless, Applicants respectfully submit that the "Declaration," at ¶ 9 through ¶ 17, provides evidence that one having ordinary skill in the art could practice the claimed invention without undue experimentation. Applicants respectfully submit that the requirements of the first paragraph of 35 U.S.C. §112 have been met.

It is settled law that whenever the adequacy of enablement provided by an applicant's specification is challenged, the Examiner has the initial burden of giving reasons, supported by the record as a whole, why the specification is not enabling. *In re Armbruster*, 185 U.S.P.Q. 152 (C.C.P.A. 1975). The enablement requirement of 35 U.S.C. §112 is satisfied if a disclosure contains sufficient information such that persons of ordinary skill in the art, having the disclosure before them, would be able to make and use the invention. The legal standard for enablement under §112

is whether one skilled in the art would be able to practice the invention without undue experimentation. *In re Wands*, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988). In this respect, the following statement from *In re Marzocchi*, 169 U.S.P.Q. 367, 369-370 (C.C.P.A. 1971), is noteworthy:

> The only relevant concern of the Patent Office under these circumstances should be over the truth of any such assertion. The first paragraph of §112 requires nothing more than objective enablement. How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance.
>
> As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirements of the first paragraph of §112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied upon for enabling support.

The law thus requires that the Patent Office accept Applicants' assertion of enablement or provide reasoning and evidence to substantiate doubts of the objective truth of Applicants' assertion.

Applicants respectfully submit that the reasoning and evidence offered in the Official Action is insufficient to support the conclusion that the claimed invention is not enabled. Moreover, the "Declaration," provided herewith pursuant to 37 C.F.R. §1.132, provides evidence that the invention claimed is enabled. In an effort to clearly put forth the reasons why a conclusion of enablement is proper, Applicants present specific responses to the points raised by the Examiner in making this rejection.

In making her rejection, the Examiner alleges at pages 3 to 4 of the Official Action that

> Applicant[s do] not teach any five, ten or fifteen amino acids of SEQ ID NO:3 which is effective for use as a vaccine. The vaccine use implies that the polypeptide would elicit a protective immune response in administered animals when challenged with wildtype *H. pylori*. The state of the prior art does not teach which polypeptides/proteins are effective for use as a vaccine against *H. pylori*. The current state of the art as of the date of this writing indicates that a mucosal adjuvant is required for vaccine efficacy of *H. pylori* component vaccines. Furthermore, even if a five, ten or fifteen amino acids of SEQ ID NO:3 is effective for use as a vaccine, Applicant provided no guidance as to which amino acids of SEQ ID NO:3 would be effective, or how one skilled in the art would be able to eliminate inoperable embodiments without undue experimentation. Applicant[s do] not teach which five, ten or fifteen amino acids of SEQ ID NO:3 "exhibits substantially no contribution to toxicity".

Applicants respectfully disagree with the Examiner's characterization of the state of the prior art, and the scope of the disclosure, as well as the requirements for enablement. Applicants further assert that the teachings in the specification provide enablement for the invention as claimed, because they provide enough direction to one of skill in the art to make and use the invention. It would have been routine, at the time the application was filed, to determine which fragments of ten or fifteen amino acids of a *H. pylori* protein would be effective in a vaccine. The "Declaration," at ¶ 11 and at ¶ 13 and ¶ 15 through ¶ 17, attests to the routine nature of determining which fragments of ten or fifteen amino acids of a *H. pylori* protein would be effective in a vaccine. At ¶ 11, the "Declaration" explains that it would have been routine to generate fragments of ten or fifteen amino acids of a *H. pylori* protein, using known recombinant techniques and the sequence information disclosed in the specification. At ¶ 13, ¶ 15, and ¶ 16, the "Declaration" describes the many animal models known at the time of filing that could have been used for routine testing of the vaccine

efficacy of fragments of *H. pylori* proteins. At ¶ 17, the "Declaration" describes Ghiara *et al.*, 1997 (Exhibit G) which shows the use of a mouse model of *H. pylori* infection to demonstrate therapeutic and prophylactic vaccine efficacy of full-length CT and CAI proteins. Fragments can be tested similarly to determine which would be effective in a vaccine.

Contrary to the Examiner's assertion, a mucosal adjuvant is not required for the generation of effective *H. pylori* component vaccines. The evidence of PCT application PCT/IB99/00851 (Exhibit H), provided with the "Declaration," shows that mucosal delivery is not required for effective *H. pylori* component vaccines, much less a mucosal adjuvant, and that intramuscular immunization provides effective protection against infection (*see* "Declaration" at ¶ 18 and ¶ 19).

Applicants assert that the determination of which regions of the CT protein exhibit "substantially no toxicity, or substantially reduced toxicity" and which regions of the CAI protein exhibit "no functional contribution to toxicity, or a substantially reduced functional contribution to toxicity," could have been readily performed by those of skill in the art, at the time of filing of the application. Generation of vectors for the synthesis of recombinant polypeptide fragments for testing would also have been routine. The specification provides ample direction for such recombinant techniques at pages 18 to 38. The "Declaration," at ¶ 11, also attests to the routine nature of generating polypeptide fragments for testing. The "Declaration," at ¶ 12 and ¶ 13, also attests to the routine nature of distinguishing cytotoxic from non-cytotoxic fragments for the CT and CAI proteins, using *in vitro* and *in vivo* assays for the assessment of toxicity.

Applicants respectfully submit that the Examiner has not met her "burden to establish a reasonable basis to question the enablement provided for the claimed invention." M.P.E.P. §2164.04, citing *In re Wright*, 999 F.2d 1557, 1562, 27 U.S.P.Q.2d 1510,1513 (Fed. Cir. 1993). Assuming, arguendo, that the Examiner has met her burden, the "Declaration" rebuts it.

As noted above, the legal standard for enablement is whether the specification provides enough guidance to one skilled in the art to make and use the claimed invention without

undue experimentation. *In re Vaeck*, 20 U.S.P.Q.2d 1438, 1444 (Fed. Cir. 1991). A properly supported showing that the disclosure entails undue experimentation is part of the Examiner's initial burden under §112, first paragraph. *In re Angstadt*, 190 U.S.P.Q. 214 (C.c.p.a. 1976). Determining whether experimentation is undue is driven by a standard of reasonableness for each case, and "a considerable amount of experimentation is permissible . . . if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *Ex parte Forman*, 230 U.S.P.Q. 546, 547 (B.P.A.I. 1986).

The specification is sufficient to enable those skilled in the art to practice the claimed invention without undue experimentation. Applicants respectfully request that the rejection of claims 40 - 50 under 35 U.S.C. §112, first paragraph be withdrawn. Patentability is determined based on the record as a whole, and factual evidence presented in declarations must be considered. *In re Alton*, 37 U.S.P.Q.2d at1583. Applicants respectfully request an affidavit under 37 C.F.R. §1.104(d)(2), if this rejection is maintained.

Rejections under 35 U.S.C. §102

Under 35 U.S.C. § 102, the standard for anticipation is strict identity. A rejection based on anticipation requires a showing that each limitation of the claim be found within a single reference (*Atlas Powder Co. v. E.I. DuPont de Nemours & Co.*, 224 USPQ 409, 411 (Fed. Cir. 1984)), either expressly or inherently. *Glaxo Inc. v. Novopharm Ltd.*, 34 U.S.P.Q.2d 1565,1567 (Fed. Cir. 1995).

Claims 38 - 49 have been rejected under 35 U.S.C. §102 as allegedly being anticipated by Cover *et al.* (1992). Applicants respectfully traverse this rejection.

The claims, as amended, are directed to (1) recombinantly produced *H. pylori* CT polypeptide, exhibiting substantially no toxicity, or substantially reduced toxicity, (2) prophylatic or therapeutic vaccines comprising an immunologically effective amount of a *H. pylori* CT polypeptide, comprising at least ten or at least 15 amino acids, capable of inducing the production

of antibodies against *H. pylori*, and exhibiting substantially no toxicity, or substantially reduced toxicity, and (3) methods of making these vaccines.

Cover *et al.* (1992) describes the purification and direct sequencing of the amino-terminal 23 amino acids of the 87 kDa vacuolating toxin of *H. pylori* strain 60190, having **toxin** activity. Cover *et al.* (1992) also describes the use of purified 87 kDa vacuolating toxin to generate a rabbit antiserum.

Cover *et al.* (1992) does not describe a recombinantly produced *H. pylori* CT polypeptide, or fragment thereof, wherein the recombinantly produced polypeptide, or fragment thereof, exhibits substantially no toxicity, or substantially reduced toxicity. Cover *et al.* (1992) does not describe a recombinantly produced *H. pylori* CT polypeptide, or fragment thereof, comprising SEQ ID NO:3, or a fragment thereof, which polypeptide, or fragment thereof comprises at least about ten or at least about fifteen amino acids, can induce the production of antibodies to *H. pylori*, and exhibits substantially no toxicity, or substantially reduced toxicity. Accordingly, Cover *et al.* (1992) does not describe a prophylactic or therapeutic vaccine comprising a *H. pylori* CT polypeptide, much less a vaccine comprising an immunologically effective amount of a recombinantly produced *H. pylori* CT polypeptide, or fragment thereof, which polypeptide, or fragment thereof, comprises at least about ten or at least about fifteen amino acids, can induce the production of antibodies to *H. pylori*, and exhibits substantially no toxicity, or substantially reduced toxicity, or a method of preparing such a vaccine.

As explained in the "Declaration" at ¶ 21, a non-toxic, recombinantly produced CT was produced using the techniques referred to in the specification (Manetti *et al.*, 1995, *Infect. Immun.* 63:4476-4480 (Exhibit A)).

Because, Cover *et al.* (1992) do not disclose or teach all of the limitations of the claimed invention, Applicants respectfully request that the rejection of claims 38 - 49 under 35 U.S.C. §102 be withdrawn.

Conclusion

For the foregoing reasons, Applicants respectfully submit that claims 38 - 51 are in condition for allowance. A notice of allowance is earnestly solicited. If the Examiner feels a telephonic interview would be helpful, she is asked to call the undersigned at 215-557-5901.

Respectfully submitted,

Date: August 3, 2000

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT: COVACCI et al.

SERIAL NO. : 09/360,934 **GROUP**: 1648

FILED: July 26, 1999 **EXAMINER**: P. Bui

TITLE: HELICOBACTER PYLORI PROTEINS USEFUL FOR VACCINES AND DIAGNOSTICS

I, Francis A. Paintin, Registration No. 19,386 certify that this correspondence is being deposited with the U.S. Postal Service as First Class mail in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

On Feb. 11, 2000

Francis A. Paintin

Francis A. Paintin Reg. No. 19,386

Honorable Assistant Commissioner
of Patents and Trademarks
Washington, DC 20231

SECOND PRELIMINARY AMENDMENT

Please amend the above-identified application as follows:

At page 49, last line, before "/" insert - - (SEQ. ID NO: 1) - -; and at page 50, first line, before ")" insert - - (SEQ. ID NO: 8) - -.

After page 61, insert the enclosed Sequence Listing as specification pages 62-80, and renumber the following pages accordingly.

REMARKS

Applicants submit herewith a sequence listing (pages 1-19) for insertion into applicants' specification. Accompanying said sequence listing is a disk in computer-readable form containing all sequences thereon.

Please do not hesitate to notify the undersigned attorney if he can be of any further assistance.

Respectfully submitted,

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Date: Feb. 11, 2000

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